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Antibacterial *in vitro* assays of new γ-aminoethers and derivatives against Gram-negative and Gram-positive pathogenic bacteria

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A growth inhibition effect against four Gram-negative (*Pseudomonas aeruginosa, Salmonella typhimurium, Klebsiella pneumoniae* and *Escherichia coli*) and three Gram-positive (*Staphylococcus aureus*, *Bacillus cereus* and *Enterococcus faecalis*) pathogenic bacteria was observed for 19 of 20 tested synthetic compounds (that is seven γ-aminoethers, nine γ-aminoalcohols and four allylamines). According to the results, the Gram-negative bacteria were the most susceptible strains toward the tested compounds. In general, the MICs of the active compounds were around 1000 ppm, while the MBCs were around 2000 ppm; however, the allylamine 8a was highlighted for its ability to inhibit *E. faecalis* at the lowest concentration found in this study (MIC = 125 ppm and MBC = 250 ppm).

Key words: Antibacterial activity, γ-aminoether derivatives, minimal inhibitory concentration, minimal bactericidal concentration, Lipinski's rule.

INTRODUCTION

Aminoethers, aminoalcohols and allylamines are related compounds with superior importance not only for their practical applications displayed by themselves but also because they have been found forming part of the structure of synthetic and naturally occurring compounds of diverse practical interest (Cavalluzzi et al., 2007; Huang et al., 2009; Kotland et al., 2011; De Risi et al., 2008; Batra and Nag, 2011; Biava et al. 1999).

Thus, a series of γ-aminoether based selective serotonin (5-HT)-reuptake inhibitor (SSRI) antidepressants (fluoxetine and paroxetine) and the selective norepinephrine (NE)-reuptake inhibitor antidepressants (tomoxetine), have been reported (Pinder and Wieringa, 1993). The naturally occurring aminoalcohol anisomycin (a potent activator of stress-activated protein kinases (JNK/SAPK) and p38 MAP kinase) (Kyriakis et al., 1994) and the phenyl/thienyl-γ-aminoalcohols **1** (direct precursors for the synthesis of fluoxetine, Ar = Ph and duloxetine, Ar = 2-thienyl), have been reported as selective serotonin reuptake inhibitors (Liu et al.,

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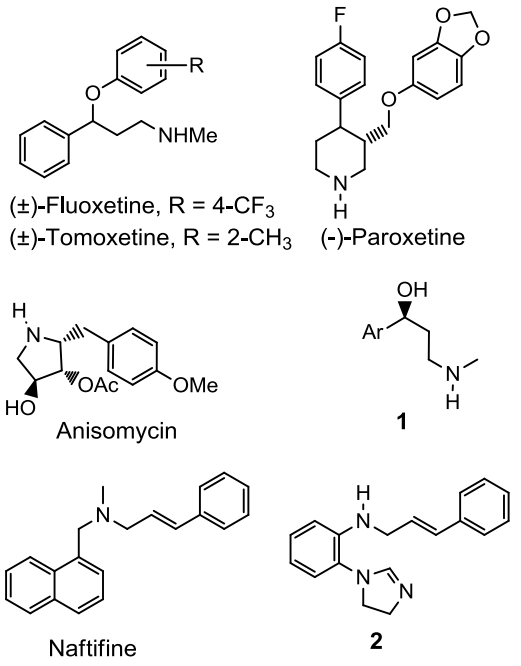


Figure 1. Some aminoethers, aminoalcohols and allylamines of biological interest.

2005). Additionally, several allylamines have been effective in topical treatments for fungal infections of the skin and nails as well as antibacterial (Crawford et al., 2000). Particularly, Naftifine hydrocloride the active ingredient of the commercially available antifungal trademark Naftin® (Jordon et al., 1990) and allylamine **2**, which shows remarkable antagonist activity against mycobacterias and fungal pathogens type *Candida* (Petranyi et al., 1981), are worthy of mention (Figure 1).

Bacteria are champions of evolution, and a few microbes have adapted to a point where they pose serious clinical challenges for humans. In addition, the ever-increasing incidence of antibiotic-resistant infections combined with a weak pipeline of new antibiotics have created a global health crisis against which, novel strategies for enhancing our current antibiotic arsenal are imperatively needed. In response to it, the last decade was characterized by a dramatic increase in the number of antibacterial agents currently under development, which is mainly driven by the urgent problem of multi-drug resistance of bacteria over several commercially available antibiotics (Arias and Murray, 2009; Brynildsen et al., 2013).

In connection with the above and continuing with our current studies on the synthetic utility of benzylamine derivatives (Abonia et al., 2010; Abonia et al., 2013a; Abonia et al., 2013b), herein, we report the preliminary studies on the antibacterial activity of recently synthesized γ-aminoethers **6**, γ-aminoalcohols **7** and allylamines 8 against several Gram-negative and Gram-positive pathogenic bacteria.

MATERIALS AND METHODS

The target compounds **6-8** were obtained by following the multicomponent approaches described in Scheme **1** (Tables 1, 2, 3 and Figure 3). The γ-aminoethers **6** were synthesized, from a four-component procedure, by stirring a mixture of amine **3** (1.0 equiv), polyformaldehyde (1.2 equiv) and the activated alkene **4** (1.0 equiv) in the corresponding alcohol **5** (3 mL) at room temperature. The γ-aminoalcohols **7** were obtained by following the same above procedure but switching alcohols 5 by acetonitrile. Allylamines **8** were obtained either from a three-component reaction in AcOH or by dehydrating the γ-aminoalcohols **7**, previously formed, in refluxing *p*-dioxane mediated by $AlCl_3$ (1 equiv) as catalyst.

Procedures for the antibacterial studies

In order to evaluate the antibacterial activity of compounds **6-8**, the following Gram-negative bacterial strains were used (*Pseudomonas aeruginosa* (ATCC® 15442), *Salmonella typhimurium* (ATCC® 13311), *Klebsiella pneumoniae* (ATCC® 31488), *Escherichia coli* (ATCC® 11229)) and Gram-positive (*Staphylococcus aureus* (ATCC® 25923), *Bacillus cereus* (ATCC® 10876) and *Enterococcus faecalis* (ATCC® 29212)) obtained from American Type Culture Collection.

Bacterial culture conditions

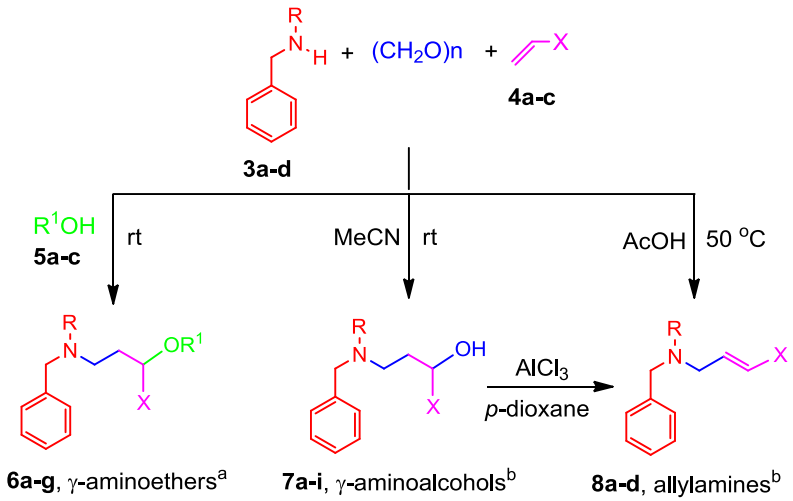
The bacterial strains were previously activated according to the manufacturer instructions and were grown in Muller-Hinton (M-H) broth to 37°C. The time necessary to reach late-exponential phase and bacterial growth were measured by optical density (540 nm), verifying the cell number by plate count. This procedure ensured that the bacterial inoculum was in the same growth phase at a cell concentration in the range of 5 to 45×10^8 CFU/mL.

Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)

The MIC is defined as the lowest concentration of antimicrobial agent (µg/mL) that will inhibit the visible growth of a microorganism after 24 h of incubation, and the MBC is the lowest concentration of antimicrobial agent that kills more than 99.9% of the viable organisms after a given incubation time (usually 24 h) (Andrews, 2001).

Broth dilution method

The method proposed by the NCCLS was used (Sisto et al., 2009; Gökçe et al., 2005; Ryan et al., 2002). For each determination a series of 5 test tubes, previously sterilized at 120°C using 15 pounds of pressure for 15 min in a horizontal autoclave, were used and set in the following order: 1.790 mL of (M-H) broth was added to the first test tube and 1 mL into each of the remaining 4 test tubes. Afterwards, 210 µL of the substance to be evaluated, which was previously diluted in DMSO to a concentration of 20000 ppm, was added to the first test tube, obtaining a concentration of 2100 ppm (without inoculum) and a total volume of 2 mL. This solution was mixed using a vortex and 1 mL of it was transferred to the second test tube. This procedure was repeated for the following tubes by transferring 1 mL from the previous tube to the next one in line. Then, each test tube was inoculated with 50 µL of culture of microorganisms in M-H, previously grown to their exponential growth phase. Therefore, the final volume for the five test tubes was 1.05 mL each one (after adding the inoculum), and their final



Scheme 1. General approach for the synthesis of the target γ-aminoethers **6**, γ-aminoalcohols **7** and allylamines **8**. [a](Abonia et al, 2013b). [b]Manuscript in preparation.

Table 1. Minimal inhibitory concentration and minimal bactericidal concentration of the γ-aminoethers **6** evaluated.

Entry	Compound	Inhibited bacteria[a]	MIC (ppm)	MBC (ppm)	Clog *P*[b]	MR (cm^3/mol)[c]	MW[d]	TNA[e]
1	**6a**	*E .coli* *K. pneumoniae* *S. typhimurium*	1000 1000 1000	2000 2000 2000	1.96	80.35	276.37	44
2	**6b**	*K. pneumoniae* *S. typhimurium*	1000 1000	2000 2000	3.69	104.85	352.47	54
3	**6c**	*E. coli* *S. typhimurium* ***E. faecalis***	1000 1000 1000	2000 2000 2000	1.44	53.01	306.40	48
4	**6d**	*E. coli* *K. pneumoniae* *S. typhimurium*	1000 1000 1000	2000 2000 2000	3.69	104.85	249.35	41
5	**6e**	*E. coli* *K. pneumoniae* *S. typhimurium*	1000 1000 500	2000 2000 1000	3.69	104.85	352.47	54
6	**6f**	*K. pneumoniae* *S. typhimurium* ***B. cereus***	1000 1000 500	2000 2000 1000	4.43	97.92	325.44	51
7	**6g**	*E. coli* *P. aeruginosa* *K. pneumoniae* *S. typhimurium*	1000 1000 1000 1000	2000 2000 2000 2000	3.37	83.03	277.40	47

[a]The bacteria names in bold correspond to Gram-positive strains, the remaining are the Gram-negative ones. [b]Calculated log of Partition coefficient. [c]Molar refractivity. [d]Molecular Weight. [e]Total number of atoms.

Table 2. Minimal inhibitory concentration and minimal bactericidal concentration of the γ-aminoalcohols **7** evaluated.

Entry	Compound	Inhibited bacteria[a]	MIC (ppm)	MBC (ppm)	Clog *P*	MR (cm^3/mol)	MW	TNA
8	**7a**	*S. typhimurium*	1000	2000	1.59	75.59	262.35	41
		E. coli	1000	2000				
9	**7b**	***S. aureus***	500	1000	3.33	100.09	338.44	51
		B. cereus	500	1000				
10	**7c**	*P. aeruginosa*	500	1000	2.25	68.87	235.32	38
		K. pneumoniae	500	1000				
		S. typhimurium	500	1000				
		S. aureus	1000	2000				
11	**7d**	*E. coli*	1000	2000	3.65	88.57	297.39	45
		P. aeruginosa	1000	2000				
		K. pneumoniae	2000	2000				
		S. aureus	1000	1000				
12	**7e**	*E. coli*	1000	2000	2.95	121.84	428.52	63
		S. typhimurium	500	1000				
		B. cereus	1000	2000				
13	**7f**	*K. pneumoniae*	1000	2000	1.93	80.39	276.37	44
		B. cereus	1000	2000				
14	**7g**	*E. coli*	1000	2000	2.33	68.67	235.32	38
		K. pneumoniae	500	1000				
		S. typhimurium	500	1000				
		E. faecalis	1000	2000				
		B. cereus	500	1000				
15	**7h**	*E. coli*	250	500	4.06	93.17	311.42	48
		P. aeruginosa	1000	2000				
		K. pneumoniae	250	500				
		S. typhimurium	250	500				
16	**7i**	*K. pneumoniae*	1000	2000	2.73	130.01	472.53	66
		S. typhimurium	1000	2000				

[a]The bacteria names in bold correspond to Gram-positive strains, the remaining are the Gram-negative ones.

concentrations were 2000, 1000, 500, 250 and 125 ppm, respectively. A test tube containing 1 mL of broth culture, without inoculum, was included as negative control. A test tube containing only broth culture and the bacterial inoculum was set as the positive control. All the above was performed in triplicate and incubated at 35°C for 24 h.

Reading of results

MIC results were reported taking into account the immediately previous test tube to the one which presented growth of microorganisms, determined by turbidity (Figure 2), or growth on plate. This last procedure was carried out when the substances caused an initial turbidity after they were added to the growth medium.

Minimal bactericidal concentration test (MBC)

From the test tubes that did not show apparent bacterial growth in the MIC experiments, 0.1 mL of solution was taken and spread in Petri dishes with M-H agar and incubated for 24 h at 37°C. Taking into account the test tube from which the inoculum was taken, the concentration of antimicrobial agent necessary for inhibiting bacterial growth was determined.

Experimental design

The experiment was carried out using a two factor design in which the first factor corresponded to the number of substances used (20) and the second, the different concentrations (5) to which the bacterial strains were exposed in this study and the experiments

Table 3. Minimal inhibitory concentration and minimal bactericidal concentration of the allylamines **8** evaluated.

Entry	Compound	Inhibited bacteria[a]	MIC (ppm)	MBC (ppm)	Clog *P*	MR (cm^3/mol)	MW	TNA
17	**8a**	***E. faecalis***	125	250	3.53	98.92	320.43	48
		B. cereus	1000	2000				
18	**8b**	*E. coli*	1000	2000	1.80	74.43	244.33	38
		P. aeruginosa	1000	2000				
		K. pneumoniae	1000	2000				
		S. typhimurium	2000	2000				
		S. aereus	1000	2000				
		B. cereus	500	1000				
19	**8c**	*E. coli*	1000	2000	2.14	79.23	258.36	41
		S. typhimurium	1000	2000				
20	**8d**	*All bacterial strains*	No inhibition	No inhibition	3.15	120.67	410.51	60

[a]The bacteria names in bold correspond to Gram-positive strains, the remaining are the Gram-negative ones.

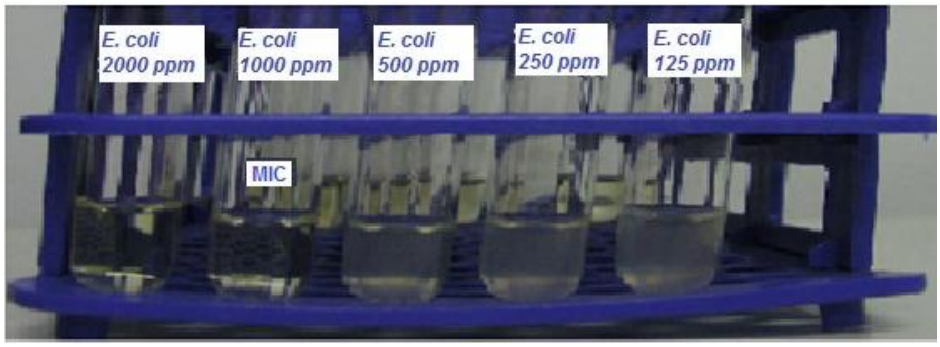


Figure 2. A representative picture for the MIC determination against Gram-negative bacteria.

were carried out by triplicate. Since the results obtained in the MIC and MBC tests were qualitative (inhibition, no inhibition), the responses corresponded to binary variables, and in addition, all the repetitions had identical results. It can be deduced that there was no observed variability in the different treatments because all the results were the same for all the repetitions; hence, it was not possible to perform a parametric inferential analysis. This fact is because, according to the method used in this work, counting of cells or colony forming units on bacterial plates, which could have some variability, is unnecessary and was not performed.

RESULTS AND DISCUSSION

Figure 3 summarizes the structure of the obtained compounds for antibacterial evaluation.

All synthesized compounds have the capability to form hydrogen bonds due to the nitrogen atom present in their structures. This feature could make it possible for them to bind to the molecules of the bacterial structure, by either allowing them to bind to the wall or external membrane and to be transported within the bacteria. A growth inhibition effect was observed for 19 of 20 tested compounds (that is γ-aminoethers **6a-g**, γ-aminoalcohols **7a-i** and allylamines **8a-c**), with the exception of the allylamine **8d** (Tables 1 to 3). In general, the minimal inhibitory concentrations (MICs) of the active substances were around 1000 ppm, while the MBCs were around 2000 ppm.

Among γ-aminoethers **6** (Table 1), all evaluated substances affected *S. typhimurium*, continued by *K. pneumoniae*, which was inhibited by six of the seven compounds with a MIC of 1000 ppm and a MBC of 2000 ppm. Compound **6g** affected all Gram-negative bacteria

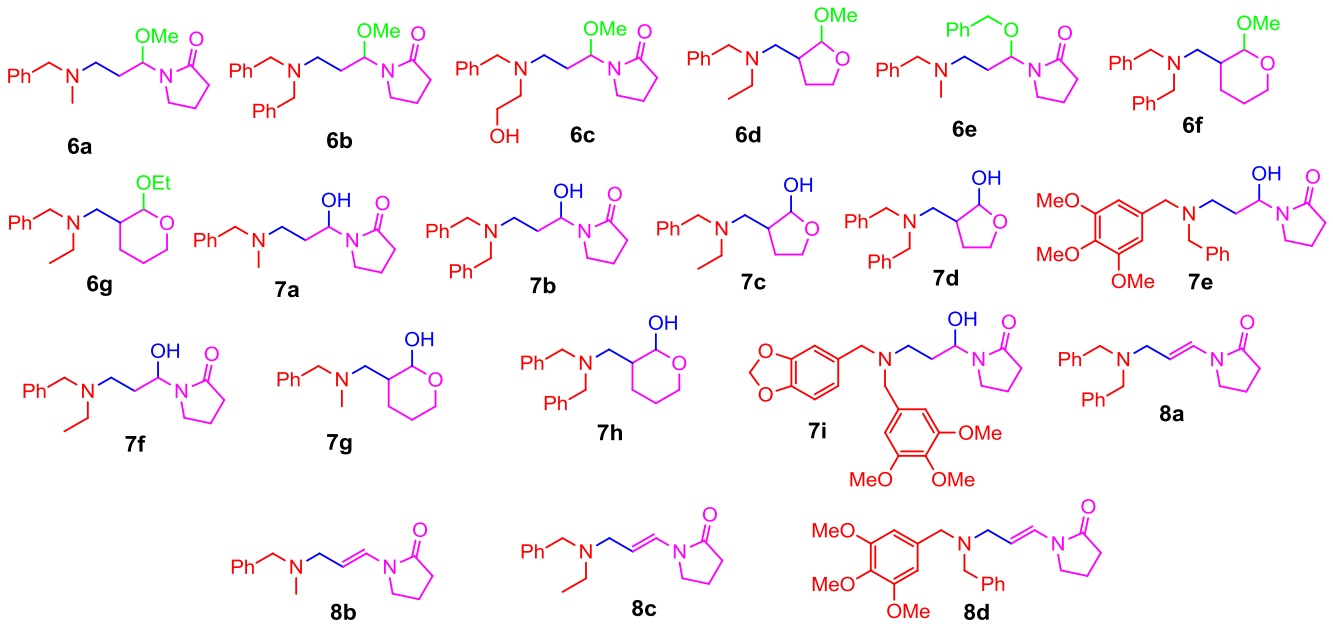


Figure 3. Chemset of the obtained γ-aminoethers **6**, γ-aminoalcohols **7** and allylamines **8** used for antibacterial tests.

with MIC of 1000 ppm and MBC of 2000 ppm. Compound **6f** was comparatively the most outstanding substance of this group because it had the relatively lowest MIC and MBC values. In Gram-positive bacteria, this group of compounds was the least effective, having presented bactericidal activity in only two (that is **6c** and **6f**) of the seven compounds which affected *E. faecalis* and *B. cereus*, respectively.

In general, γ-aminoethers **6** were noted for their bactericidal action against Gram-negative bacteria, because out of the seven compounds tested, five of them (**6a**, **6d**, **6e**, **6f** and **6g**) exhibited antibiosis against this family of microorganisms. Moreover, the most susceptible strain toward the γ-aminoethers **6** (*S. typhimurimum*), which was inhibited by all compounds **6**, showed that this bacterium was particularly susceptible to the benzyl groups present in such structures.

On the other hand, all nine evaluated γ-aminoalcohols **7** showed inhibitory effects on the studied bacteria, being the greatest inhibition against Gram-negative bacteria. Among them *K. pneumoniae* and *S. typhimurium* were susceptible to six of the nine compounds **7**, while *E. coli* was sensible to five of them (Table 2). Compounds **7g** and **7h** are highlighted, the first one, for inhibiting a greater number of bacterial strains Gram-negative as well as Gram-positive, and the second one, for presenting the lowest MICs (250 ppm) and MBCs (500 ppm) values of this group, affecting the growing of all the studied Gram-negative bacteria, although it did not affect any of the Gram-positives. Gram-positive bacteria showed a higher resistance to these types of compounds; *B. cereus* was affected by four compounds, *S. aureus* by three and *E. faecalis* by only one of them (Table 2).

It was also observed, that some functional groups in **7** determined the biological activity of these molecules. That is how a different behavior was observed for each of the nine tested compounds **7** when the substituents were pyran, pyrrolidone or furan. Although, this group of compounds was the most active, since all of them showed bactericidal effect against at least one strain of the study, apparently, the presence of pyran and benzyl groups simultaneously in the molecule was the better combination for the widest spectrum of activities and lowest MICs and MBCs values as shown by compounds **7g** and **7h** (Table 2).

With regard to allylamines **8**, from the four compounds that were evaluated (**8a-d**), three of them showed any type of activity (Table 3). Compound **8b** achieved growth inhibition for six of the seven evaluated bacterial strains, while, compound **8a** presented the lowest MIC (125 ppm) as well as the lowest MBC (250 ppm) from all studied compounds by negatively affecting *E. faecalis*, although it did not show any effect on the Gram-negative strains. Particularly, allylamine **8d** was the unique compound which did not present any antibiosis against any bacteria in this study.

Moreover, for allylamines, when R was a benzyl group (i.e. **8a**), only Gram-positive bacteria were affected; but when it was a methyl (**8b**), the spectrum of action was broadened to include the Gram-negative bacteria also (Table 3). In contrast, the inactivity observed for compound **8d** (structurally analogue to **8a**) should be associated with the presence of the methoxyl groups in the R substituent, which could not contribute to its

lipophilicity and hence to its bactericidal activity.

It is known that the Lipinski's rule ("the rule of 5") is a qualitative rule published in 1997 based on parameters such as log *P* (Partition coefficient), molar refractivity (MR), molecular weight (MW), total number of atoms (TNA) and number of donors/acceptors hydrogen bonding to predict the lipophilicity of a small molecule associate with its poor or good permeation/absorption capability to cross the cell wall and for instance determine its activity (Lipinski et al., 1997; Leo et al., 1971). Subsequently, Ghose et al. (1999) inspired by Lipinski's rule, performed a qualitative and quantitative characterization of known drugs based on Comprehensive Medicinal Chemistry (CMC) databases, which included some central nervous system active drugs and cardiovascular, cancer, inflammation, and infection disease states (including several antibacterials). The study afforded average values for the aforementioned parameters (calculated log *P* (Clog *P*) = 2.52, MR = 97, MW = 357, and TNA = 48) for the different classes of drug molecules studied. Additionally, benzene was the most abundant structural unit found in such drug database (Ghose et al., 1999).

Tables 1, 2 and 3 show the values of Clog *P,* molar refractivity, molecular weight and total number of atoms determined for all twenty compounds in our study (Calculated octanol-water, 2014). A raw comparative analysis suggests compounds **6f**, **7h** and **8a** as relatively more active in their corresponding series because of their comparatively lower values of MIC and MBC. The Clog *P*, MR, MW and TNA values were 4.43, 97.92, 325.44 and 51; 4.06, 93.17, 311.42 and 48 and 3.53, 98.92, 320.43 and 48 for compounds **6f**, **7h** and **8a** respectively. Interestingly, several values of the above four parameters, match better with some of the average values (2.52, 97, 357 and 48) determined by Ghose et al. (1999) than those for the remaining compounds of the studied series. This means that there is relative agreement between the Lipinski´s rule parameters and the activity found for the more active compounds **6f**, **7h** and **8a** of the three series **6**, **7** and **8** respectively. Moreover, all three compounds possess the dibenzylamino moiety (two free phenyl groups content) which are in agreement with findings by Ghose et al. (1999).

Finally, it is worth mentioning that *P. aeruginosa* is one of the leading Gram-negative organisms tightly associated with nosocomial infections and their consequences for immunocompromised patients. The increasing frequency of multi-drug-resistant *P. aeruginosa* (MDRPA) strains confirms that efficacious antimicrobial options for their treatment are currently limited (Obritsch et al., 2005). In this sense, the fact that five of the evaluated compounds (**6g**, **7c**, **7d**, **7h** and **8b**) were active (although in moderate strength, MIC´s = 500-1000 ppm), it is a remarkable finding because of the current urgency for new active drugs against these kind of pathogens. Our modest results could be a starting point for this purpose.

Conclusion

In summary, the evaluated substances showed differential antibacterial activity between both strains, showing that the Gram-negative bacteria were the most susceptible ones. Indeed, *S. typhimurium*, *K. pneumoniae*, *E. coli* and *P. aeruginosa* were sensible to 15, 13, 12 and 5 of the evaluated compounds, respectively. Meanwhile, Gram-positive bacteria were more resistant, according to the observed behavior in *B. cereus*, *S. aureus* and *E. faecalis*. They were affected by 7, 4 and 3 of the evaluated compounds respectively, which produced a negative effect on their growth. The allylamine **8a** is highlighted for its ability to inhibit *E. faecalis* at the lowest concentration found in this study, with a MIC of 125 ppm and a MBC of 250 ppm. The four parameter values (that is, Clog *P*, molar refractivity, molecular weight and total number of atoms) for the more active compounds **6f**, **7h** and **8a**, were in relative agreement with the Lipinski´s rule and the qualitative/quantitative characterization of known drugs database performed by Ghose and co-workers.

Although it was not possible to establish a rigorous activity-structure relationship due to the relative high MIC and MBC values, certainly, it can be assumed that some functional groups in compounds **6**, **7** and **8** could be responsible for their biological activities.

Conflict of interests

The authors did not declare any conflict of interest.

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